Importance of the knowing and means of measuring the diffusion coefficient activation energy of elastomer closures

Ivette Novoa, MSc
Cuba

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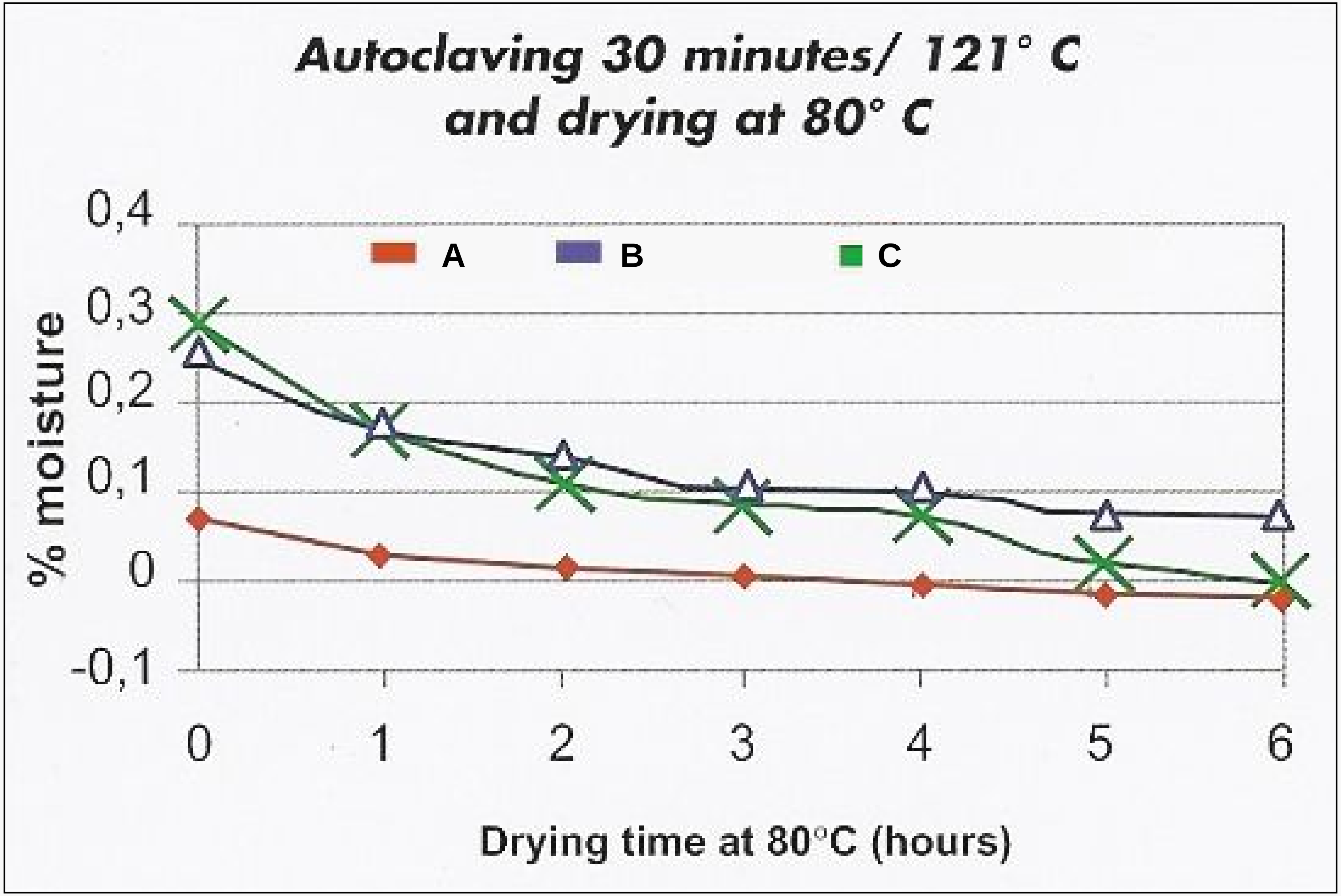
COMMON PROCESS ON PHARMACEUTICAL INDUSTRY

WHAT IS COMMONLY DONE?

POST – STERILIZATION DRYING PROCESS

- **Making pulse of vacuum in the own autoclave**
- **Drying stoppers in common dry heat sterilizers, heating the stoppers at the maximum allowable temperature for the specific elastomeric material during a long time.**

DATA COMMONLY FOUND



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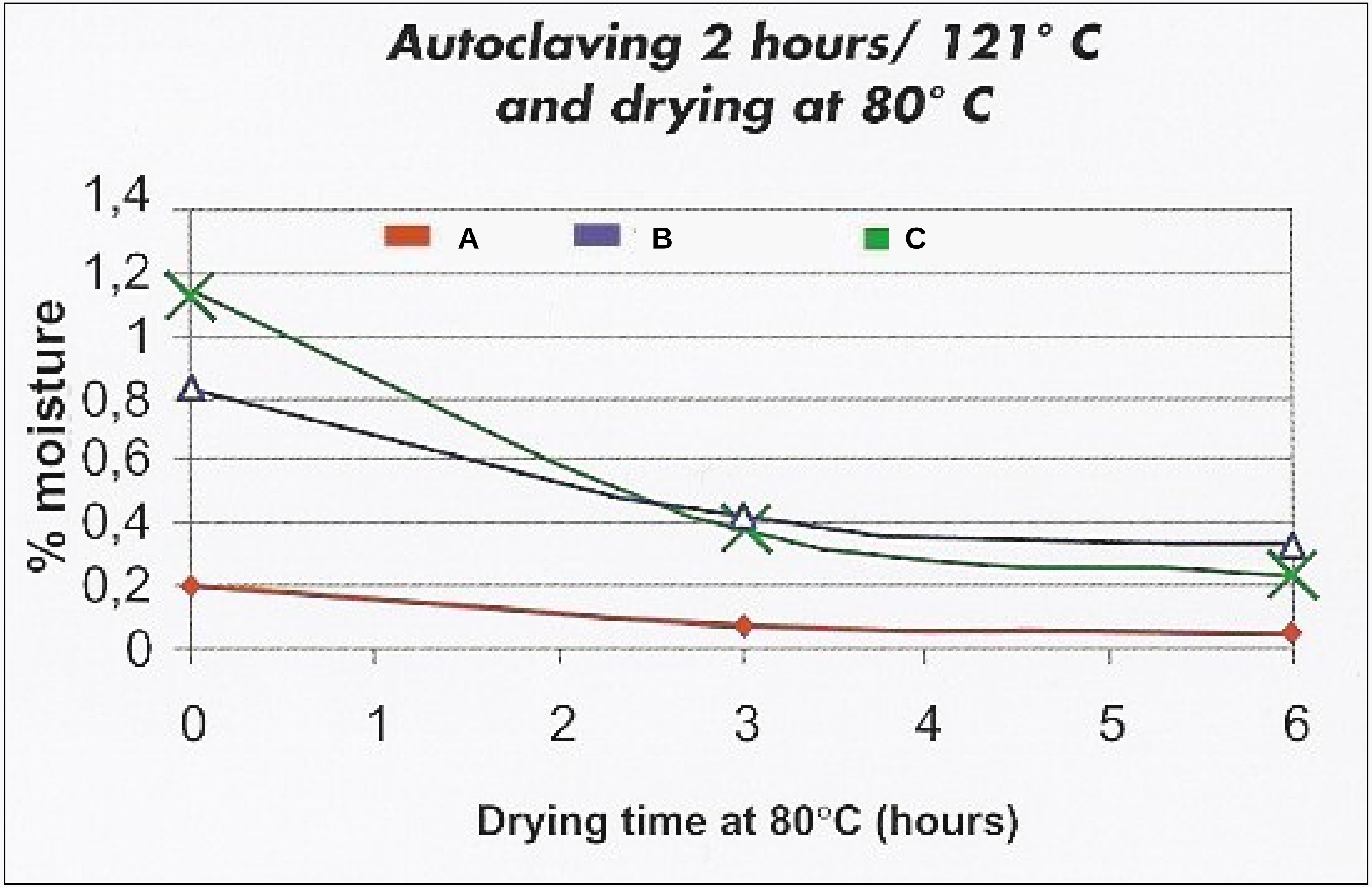
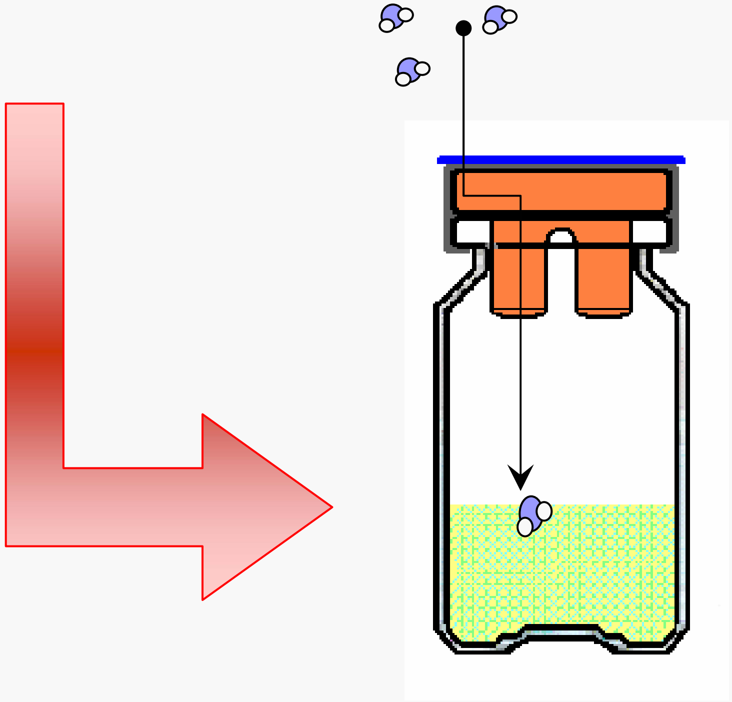


PERMEATION VS. OUTGASSING

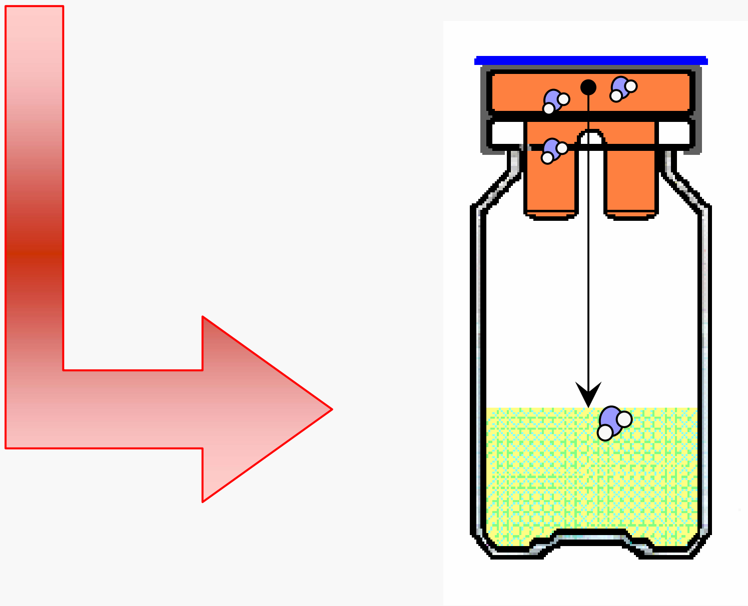
PERMEATION

Is dependent on temperature and the difference in the partial pressure of water vapor in the atmosphere and that in the sealed container



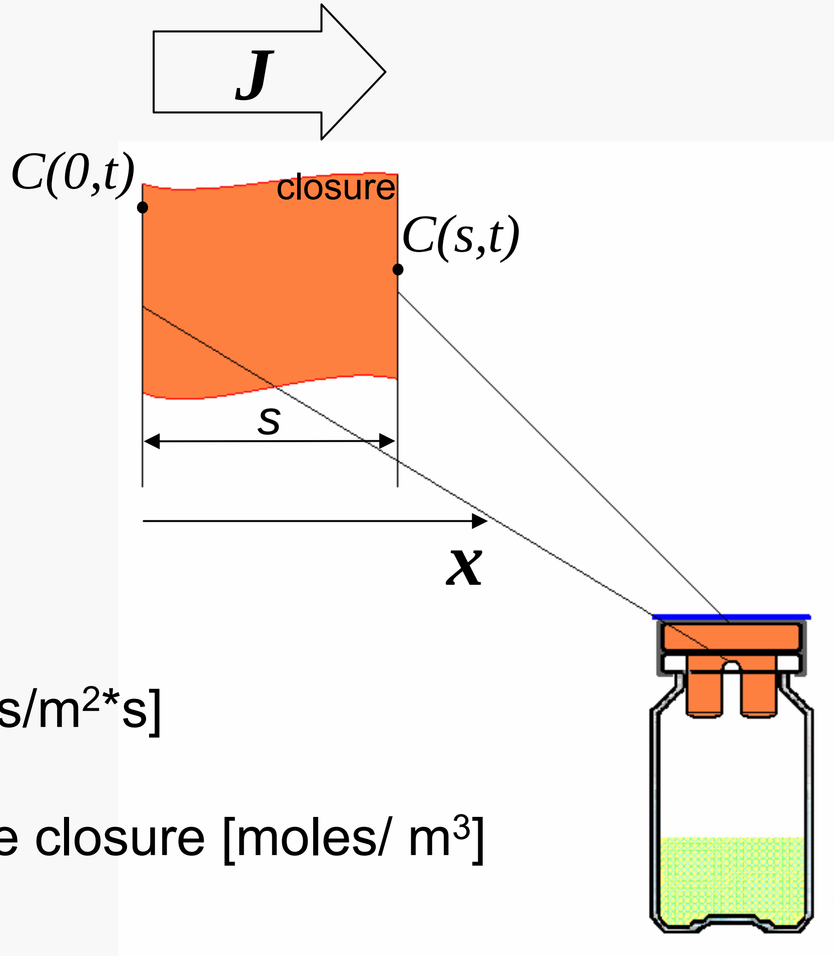
OUTGASSING

Is also temperature dependent, but it is independent of the ambient humidity and is dependent of the moisture in the stoppers.



Flick´s First Law of Diffusion

(1) $$J = -D \frac{dC(x,t)}{dx}$$



Where:

→J is the flux of water molecules [moles/m^2*s]
→D is the diffusion coefficient [m^2/s]
→C is the concentration of moisture in the closure [moles/ m^3]
→x is a position in the closure
→t is the time

Flick´s Second Law of Diffusion

$$J = -D\frac{dC(x,t)}{dx}$$

(2) $$\frac{dC(x,t)}{dt} = -\frac{dJ}{dx}$$

Replacing 1 in 2

(3) $$\frac{dC(x,t)}{dt} = D\frac{d^2C(x,t)}{dx^2}$$

Diffusion Coefficient

$$D = D_0 \cdot e^{-\frac{Ea}{R \cdot T}} \qquad \textbf{(4)}$$

→Where:
→Do is the maximum diffusion coefficient
→Ea is the activation energy [kcal/mol]
→T is the temperature [K]
→R is the gas constant

Mathematical Calculations

$$D = D_0 \cdot e^{-\frac{Ea}{R \cdot T}}$$

$$\frac{dC(x,t)}{dt} = D \frac{d^2C(x,t)}{dx^2}$$

Replacing 4 in 3

$$\frac{dC(x,t)}{dt} = D_0 \cdot e^{-\left(\frac{Ea}{R \cdot T}\right)} \cdot \frac{d^2C(x,t)}{dx^2}$$

As *dC(x,t)/dt* is the Outgassing rate (*v(x,t)*), then:

(5)

$$v(x,t) = D_0 \cdot e^{-\left(\frac{Ea}{R \cdot T}\right)} \cdot \frac{d^2C(x,t)}{dx^2}$$

Mathematical Calculations

Equation (5) can be expressed as:

(6) $$\ln\left(v(x,t)\right) = \ln D_0 - \frac{Ea}{R \cdot T} + \ln\left(\frac{d^2C(x,t)}{dx^2}\right)$$

Being a lineal plot as:

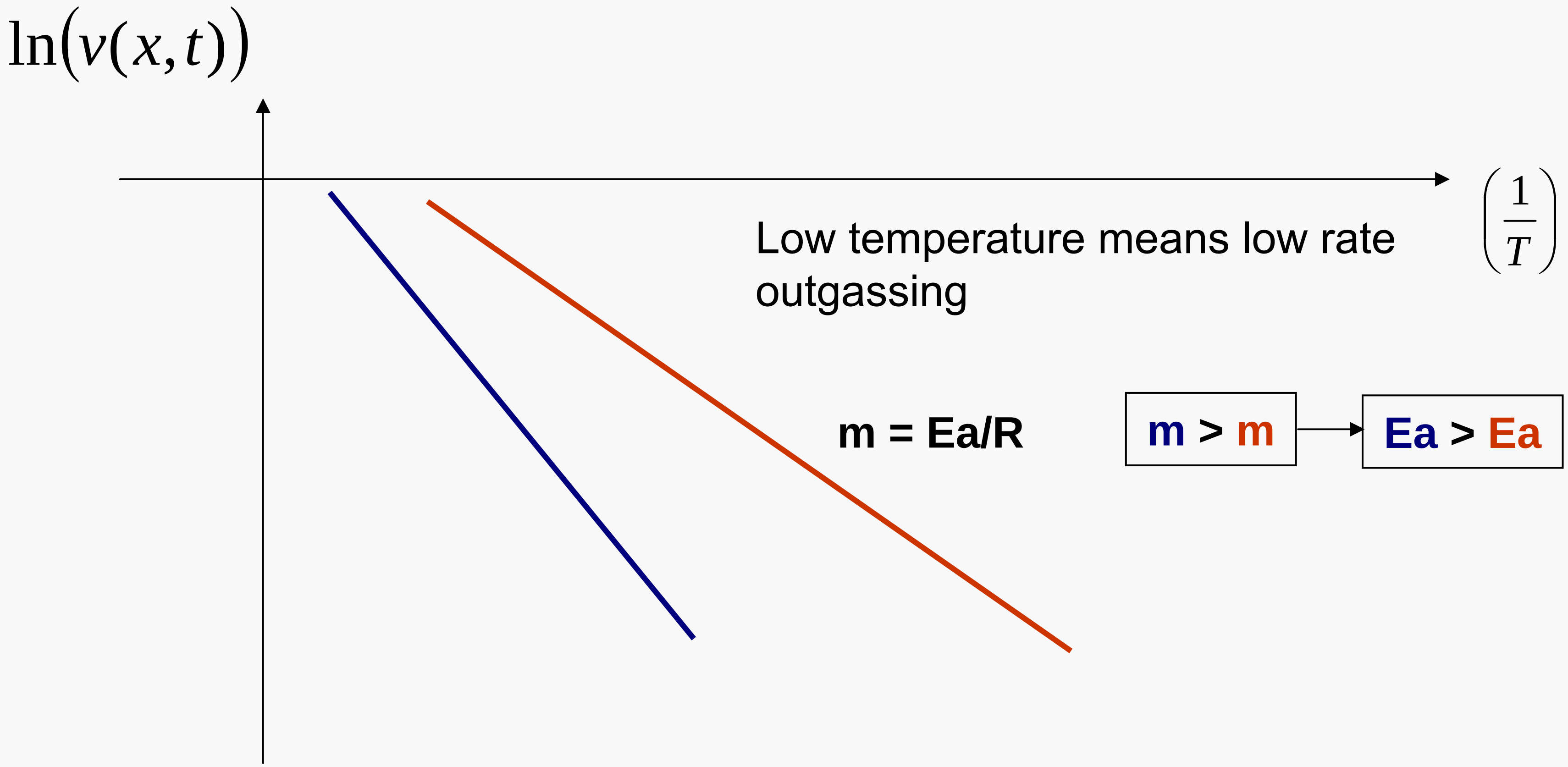
$$\underbrace{\ln\left(v(x,t)\right)}_{y} = \underbrace{\ln D_0 + \ln\left(\frac{d^2C(x,t)}{dx^2}\right)}_{n} - \underbrace{\frac{Ea}{R \cdot T}}_{m} \cdot x$$

$y = n - m \cdot x$

Mathematical Calculations

$$\underbrace{\ln\left(v(x,t)\right)}_{y} = \underbrace{\ln D_0 + \ln\left(\frac{d^2C(x,t)}{dx^2}\right)}_{n} - \frac{Ea}{\underbrace{R \cdot T}}$$

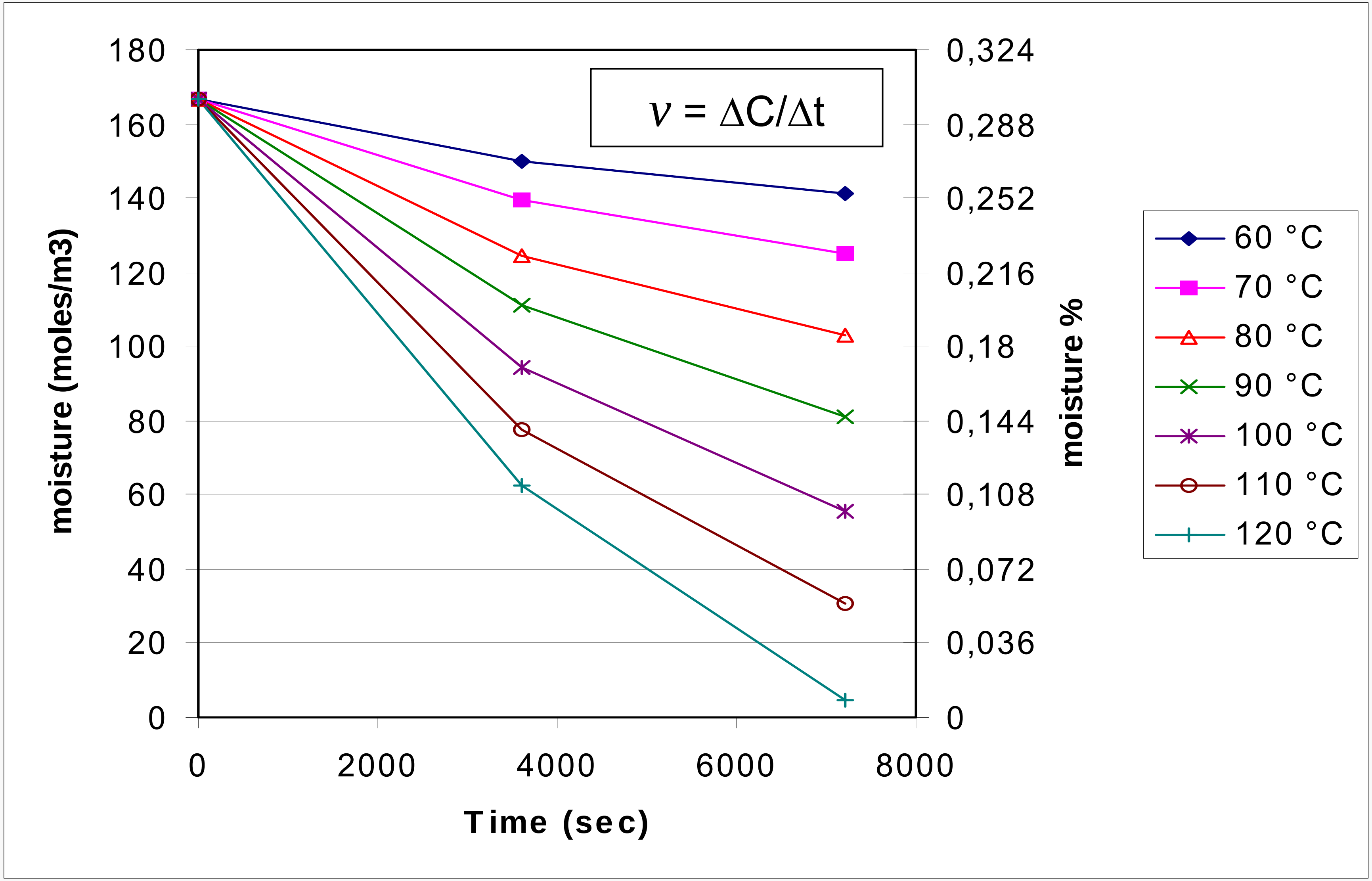
$$y \quad = \quad n \quad - \quad m \cdot x$$



Methodology

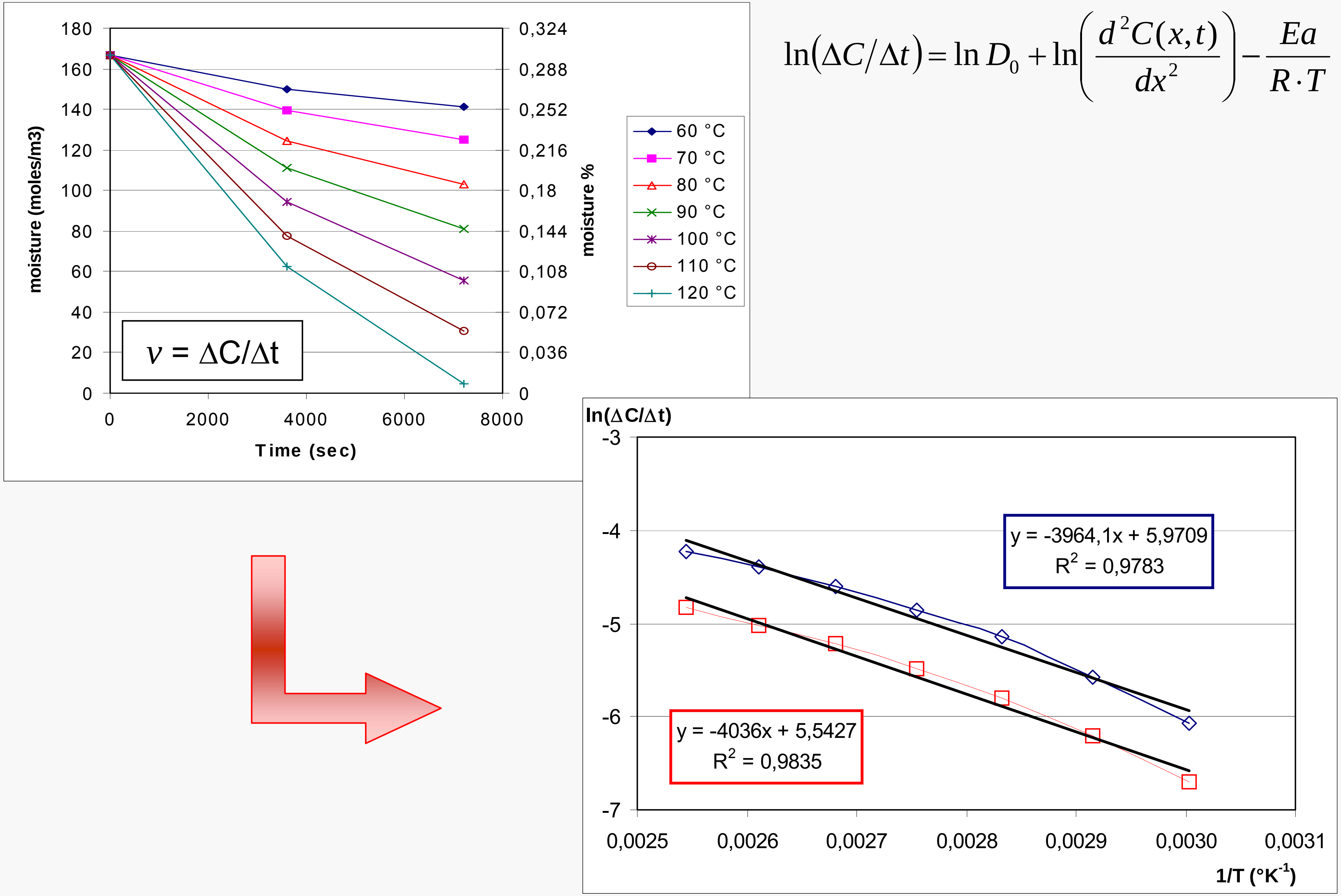
1. Measure moisture to the entire bag of closures as they are received from the manufacturer
2. Steam sterilize the same closures while sealed in the bag - this is the base line.
3. Measure moisture to the same entire bag of sterilized closures.
4. Replace the closures in a sealed bag and place them in an oven till dry temperature be T1 = 50 °C, for a specified period of time, e.g one hour.
5. Stop the drying and allow the closures to cool down till ambient temperature. Measure moisture to the entire bag of stoppers.
6. Repeat steps 4 and 5 for 60 °C, 70 °C, 80 °C, 90 °C, 100 °C, or more, till the maximum temperature which a determined elastomeric formula can resist at dry heat conditions.
7. Plot ln ($\Delta C/\Delta t$) as a function of 1/T.
8. Calculate de Ea from slope.

Plot moisture vs time at different temperatures



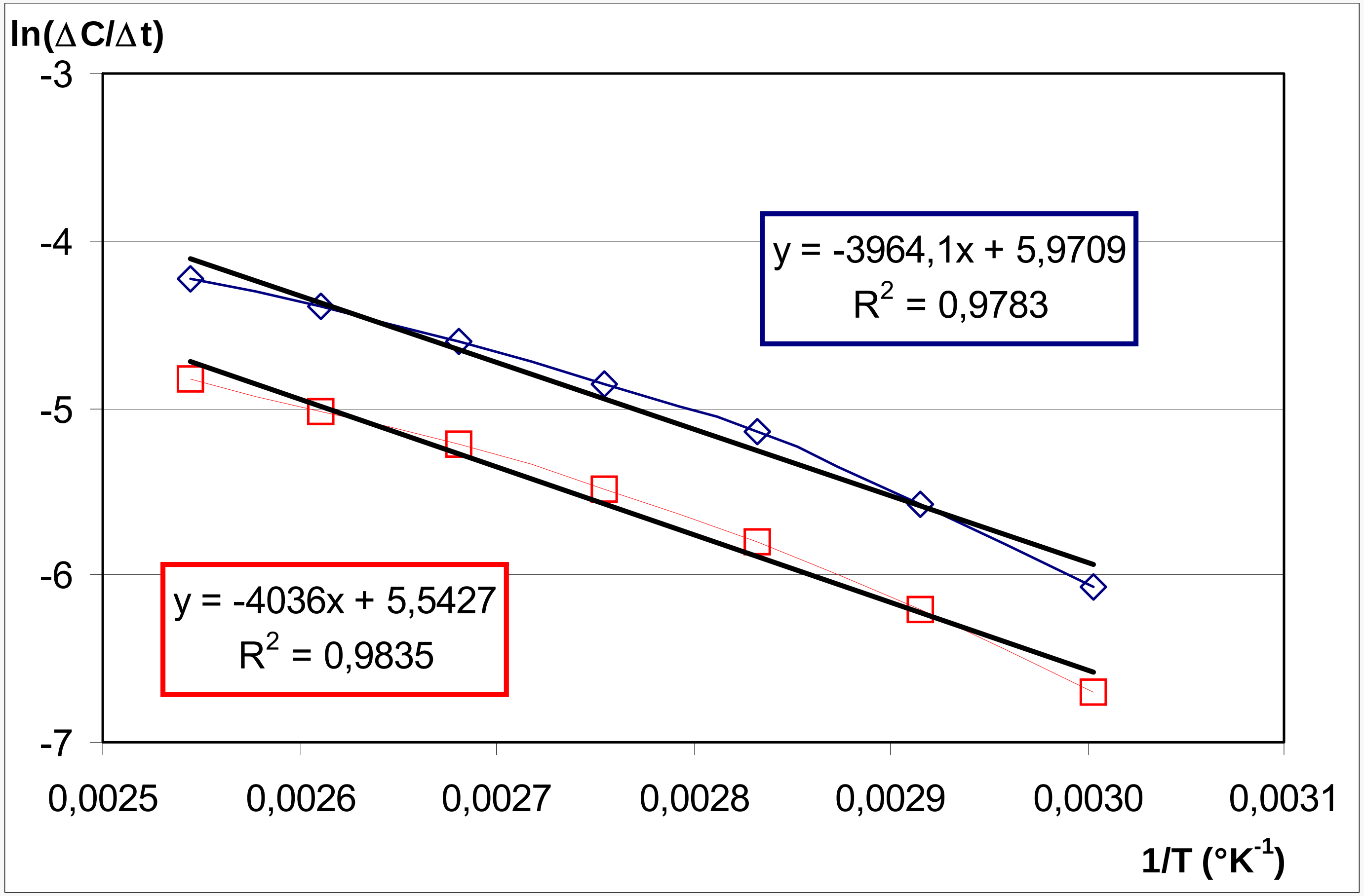
Plot moisture vs time at different temperatures

$$\ln(\Delta C/\Delta t) = \ln D_0 + \ln\left(\frac{d^2C(x,t)}{dx^2}\right) - \frac{Ea}{R \cdot T}$$



ln (ΔC/Δ t) as a function of 1/T

$$\underbrace{\ln(\Delta C/\Delta t)}_{y} = \underbrace{\ln D_0 + \ln\left(\frac{d^2C(x,t)}{dx^2}\right)}_{n} - \underbrace{\frac{Ea}{R\cdot T}}_{m\cdot x}$$



m = Ea/R

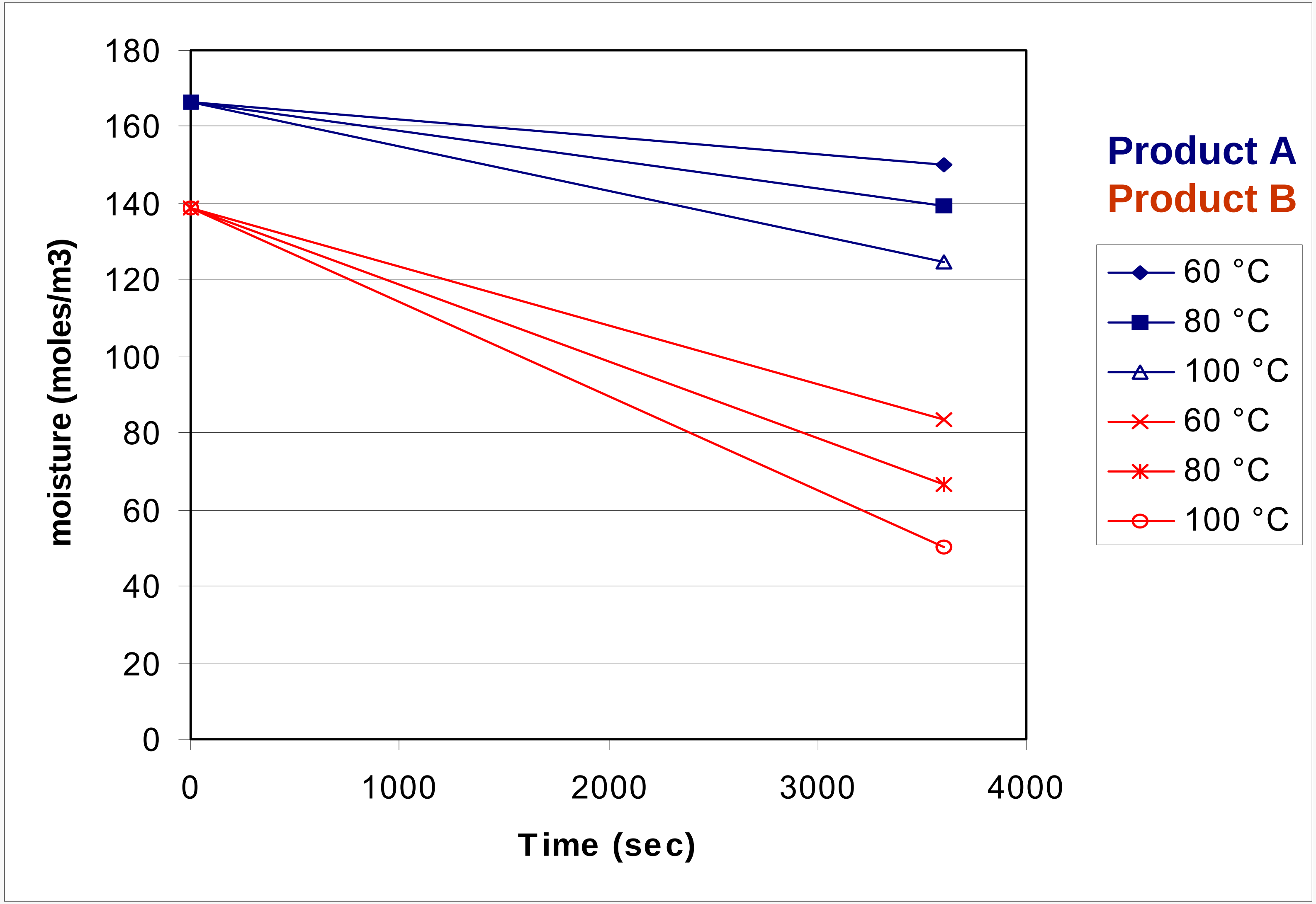
Ea = mR

m = 3790.5 K

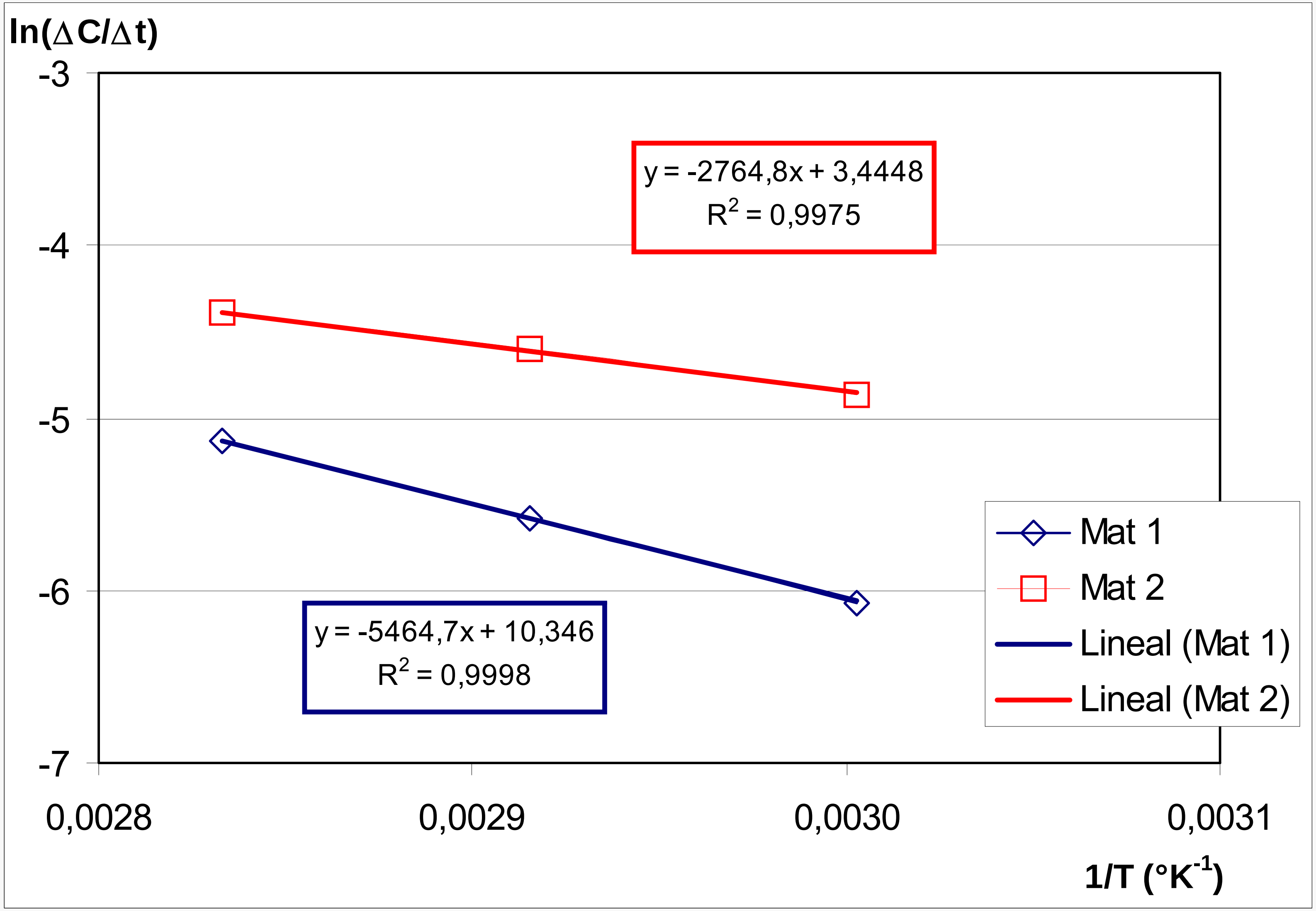
R = 8.31 J/molK

Ea = 31.5 kJ/mol

Plot moisture vs time at different temperatures (diferents products)



ln (ΔC/Δ t) as a function of 1/T (diferents products)



IMPORTANCE OF THIS STUDY

1. Small dosage forms are more costly than bigger dosage forms. This trend will force manufacturers of lyophilized products to pay more attention not only to how they dry their closures but the selection of the proper closure for lyophilization.
2. PAT as a driving force. Since new products will be costly, drug companies will want to reduce the number of defects as a result of the lyophilization process. What would be worse than to reduce the number of defective lyophilized products and then have it destroyed by moisture from the closure?

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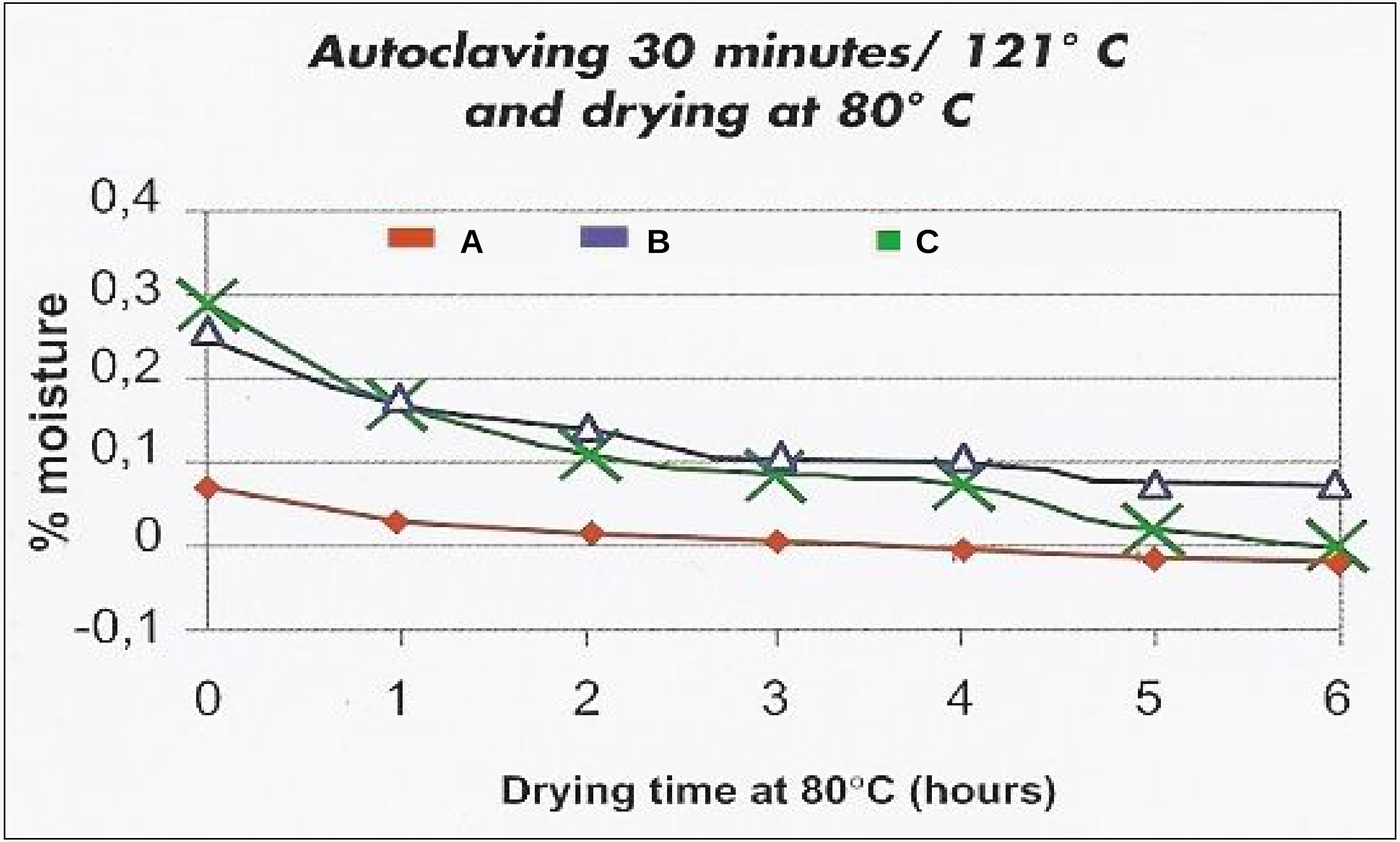

CONCLUSIONS

1. Those stoppers having higher activation energy are more difficult to dry, because the outgassing rate is lower, but at the same time they could absorb lower water during sterilization.
2. Activation energy is a fundamental property which can be used to determine when a elastomeric material is good enough to be used in lyophilized products.
3. Through proposed methodology is possible to determine if there is an activation energy value from which we can conclude what are the better elastomeric materials to be used.